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Award Number: DAMD17-01-1-0129

TITLE: New Approaches for Early Detection of Breast Tumor Invasion or Progression

PRINCIPAL INVESTIGATOR: Yan-Gao Man, M.D., Ph.D.

CONTRACTING ORGANIZATION: American Registry of Pathology
Washington, DC 20306

REPORT DATE: August 2005

TYPE OF REPORT: Annual Summary

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
01-08-2005	Annual Summary	23 Jul 2001 – 22 Jul 2005

4. TITLE AND SUBTITLE

New Approaches for Early Detection of Breast Tumor Invasion or Progression

5a. CONTRACT NUMBER

5b. GRANT NUMBER
DAMD17-01-1-0129

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Yan-Gao Man, M.D., Ph.D.

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

American Registry of Pathology
Washington, DC 20306

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

This project assessed potential roles of myoepithelial (ME) cells in breast tumor invasion, and found that a subset of pre-invasive breast tumors contained focally disrupted ME cell layers. Compared to adjacent cells within the same duct, cell clusters overlying these focal ME layer disruptions showed several unique features, including a loss of estrogen receptor expression, a significantly higher rate of proliferation, genetic instability, expression of tumor invasion and metastasis related genes, and infiltration of leukocytes. Together, our findings suggest that [1] focal ME layer disruptions might represent an early sign of tumor invasion, [2] cell clusters overlying focal ME layer disruptions might represent precursor of invasive lesions, and [3] focal ME layer disruption may result from a localized degeneration of aged or injured ME cells and resultant immunoreactions. This project is completed ahead the schedule. The outcomes of this project are expected to generate a total of 98 scientific publications (74 have been published or accepted for publication).

15. SUBJECT TERMS
Breast tumor invasion; Breast tumor progression; Myoepithelial cells; Early detection; Precursor of invasive breast cancer; Estrogen receptor expression; inflammatory cell infiltration

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(include area code)*
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Introduction

To assess interactions between epithelial (EP) and myoepithelial (ME) cells in association with breast tumor progression and invasion, a double immunostaining technique with antibodies to smooth muscle actin (SMA) and estrogen receptor (ER) was used to elucidate both the ME and EP cells in mammary tissues harboring ductal carcinoma in situ. Single or clusters of EP cells with a marked diminution or a total loss of ER expression were found immediately overlying focally disrupted ME cell layers, in contrast to the dominant population of ER (+) cells within the same duct that showed no associated ME cell layer disruptions. This study attempted to confirm our previous findings on a larger number of cases, and to compare the immunohistochemical and molecular biological profiles of the ER (-) cells overlying disrupted ME cell layers with those of adjacent ER (+) cells and surrounding stromal (ST) cells. Since ME cell layers are physical barriers protecting the microenvironment and integrity of EP cells, and the disruption of ME cell layers is an absolute pre-requisite for breast tumor invasion, the outcomes of this project could have significant values in early detection of breast tumor progression and/or invasion.

Body

a: Statement of work

A total of 7 tasks were listed in the Statement of Work of the original proposal:

Task 1. To repeat our previous studies and to identify epithelial (EP) cells overlying disrupted myoepithelial (ME) cell layers (months 1-6)

Completed: The outcomes had been published (please see attached "References-publications: # 4,5 (papers), and #1-8 (abstracts).

Task 2. To compare the biological behavior of cells overlying a disrupted ME cell layer with that of adjacent cells within the same duct (months 6-9)

Completed: The outcomes had been published (please see attached "References-publications: # 9,10, 12 (papers), and #1-8 (abstracts).

Task 3. To microdissect phenotypically different EP cells and the surrounding ME and stromal (ST) cells for molecular biological analyses (months 9-12)

Completed: The outcomes had been published (please see attached "References-publications: # 4,5 (papers), and #9-16 (abstracts).

Task 4. To compare the frequency and pattern of loss of heterozygosity (LOH), and clonality among EP, ME, and ST cells (months 12-20)

Completed: The outcomes had been published (please see attached "References-publications: # 6-10 (papers), and #16-27 (abstracts).

Task 5. To assess the gene expression pattern in cells from frozen section sections with cDNA expression array technique, and to generate probes based on sequences exclusively or mainly expressed in cells overlying disrupted ME cell layers (months 20-24)

Completed: The outcomes had been published (please see attached "References-publications: # 14-19 (papers), and #28-50 (abstracts).

Task 6. To apply the probes to both paraffin and frozen sections, to identify the gene expressing cells and their morphologic features (months 24-32)

Completed: The laboratory procedures have been completed and the outcomes are in the process of summarization for publication (please see attached "References-Scientific papers near completion or in preparation, #1-24).

Task 7. To correlate the laboratory findings with that of clinical following-up data (months 32-36).

Completed: The laboratory procedures have been completed and the outcomes are in the process of summarization for publication (please see attached "References-Scientific papers near completion or in preparation, #1-24).

b: Experimental procedures:

Consecutive sections were made from formalin-fixed, paraffin-embedded breast tissues from over 400 patients with various grades of ductal carcinoma in situ (DCIS), and double imunostained for ER and SMA. Cross sections of all ducts lined by ≥ 40 EP cells were examined for a focal ME cell layer disruption, defined as an absence of ME cells, resulting in a gap equal to or greater than the combined size of 3 EP or ME cells. A focal loss of ER expression was defined as marked diminution or a total loss of ER staining in cells immediately overlying a disrupted ME cell layer, in contrast to strong ER expression in adjacent cells within the same duct.

After immunostaining for ER and SMA, cells overlying disrupted ME cell layers, adjacent ER (+) cells within the same duct, adjacent stromal (ST) cells, and other controls were microdissected for DNA extraction and assessment for loss of heterozygosity (LOH) and microsatelite instability (MI), using PCR amplification with a panel of DNA markers at 6 chromosomes. The frequency and pattern of LOH and MI among samples were compared.

Consecutive sections were also prepared from frozen breast tissues of patients with DCIS and invasive ductal carcinomas (IDC), and were double immunostained for ER and SMA. Immunostained sections were examined for ER expression and focal ME cell layer disruptions. ER (-) cells overlying disrupted ME layers and adjacent (+) cells within the same duct in DCIS, along with morphologically and immunohistochemically similar cells in IDC, were microdissected for RNA extraction, using the RNA extraction kits from Arcturus Engineering, Inc (Mountain View, CA). The RNA extracts were subjected to RT PCR amplification. The gene expression profiles among samples were compared, using the software and reagents from Affymetrix, Inc (Santa Clara, CA) and SuperArray Bioscience Corporation (Frederick, MD).

A total of 7 biotin-labeled probes and detection kits from our collaborators, DAKO Corporation (Carpinteria, CA), and Sigma (St. Louis, MO) had been used in both paraffin-embedded and frozen sections from selected cases. The experimental procedures had been completed and several manuscripts are in preparation to report the results (see "References"-Scientific papers near completion of in preparation).

The clinical follow-up data from 50 cases with focally disrupted ME cell layers had been compared to those from 50 cases without ME cell layer disruptions, and several manuscripts are in preparation to report the results (see "References"-Scientific papers near completion of in preparation).

All above experimental procedures were carried out according to the methods described in the proposal without any major modifications. Also, all the laboratory efforts have been strictly adhered to address the issues listed in "Statement of Work".

Key research accomplishments

All the laboratory procedures for Tasks 1 to 7 had been completed, and the outcomes have been either published or in the process of preparation for publication (see below).

The outcomes of this project have generated 74 published or accepted research papers (n=21), abstracts (n=50), and figures (n=3), as well as 24 submitted (n=5), to be submitted within a month (n=2), and partially completed (n=17) research papers.

Based on his own and other findings, this PI has proposed a new hypothesis for breast and prostate tumor invasion. The hypothesis and supportive data have been recently published in several peer-reviewed journals, including Breast Cancer Research, Breast Cancer Research and Treatment, Experimental Cell Research, Cancer Detection and Prevention, and Applied Molecular Morphology & Immunohistochemistry (see attached "References": Scientific papers published, accepted, and submitted #5, 10, 12-14).

Several molecules exclusively or mainly expressed in ER negative cell clusters overlying focally disrupted ME cell layers have been identified and characterized, and is in the process for potential development of early detection or therapeutic agents.

Reportable outcomes

A total of 98 research papers (n=45), abstracts (n=50), and figures (n=3) are expected to be generated by this projects (see the "References" below).

Conclusions

1. Tasks 1-7 listed in the proposal have been completed.
2. A total of 98 publications are expected to be generated by this project.
3. The outcomes are in a total agreement with the original hypotheses in the proposal.
4. Several new molecules associated with tumor progression or invasion have been identified.

References

A. Honors and Awards:

1. A invited speaker at the Department of Chemistry and Biochemistry at Florida State University in June, 2003
2. Author of one of the best poster presentations at the 7th International Symposium on Predictive Oncology & Intervention Strategies. Nice, France, February 7-10, 2004.
3. Author of one of the best oral presentations at the 7th International Symposium on Predictive Oncology & Intervention Strategies. Nice, France, February 7-10, 2004.
4. A distinguished lecturer at Department of Defense, Center for Prostate Disease Research, October 6, 2004.
5. A invited speaker at the 3rd Annual Drug Discover & Development-Asian-Pacific Congress, June 1-3, 2005, Singapore.
6. Invited reviewer for Cancer Therapy in 2004 (one manuscript).

7. Invited reviewer for Cancer Detection and Prevention in 2004 and 2005 (three manuscripts).
8. The PI's work and picture were posted in the AFIP Letter 162 (6): 3, 2004.

B. Research grants:

1. Author and recipient of AFIP/ARP joint research initiative grant (05AA) in 2005
2. Author and recipient of "Hypothesis Development Award" (PC051308) from Congressionally Directed Medical Research Program in 2005
3. Co-investigator and co-recipient of a grant from Susan Komen Breast Cancer Foundation in 2005

C. Patent:

Co-invent of a filed patent (with Dr. Patricia E. Berg of the George Washington University)

D. Publications:

a. Scientific papers published, accepted, and submitted:

1. Bratthauer GL, Moinfar F, Stamatakos M, Mezzetti TP, Shekitka KM, Man YG, Tavassoli FA. Combined E-Cadherin and high molecular weightt cytokeratin immunoprofile differentiates lobular ductal, and hybrid mammary intraepithelial neoplasias. Human Pathol 33: 620-627, 2002
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Implications for tumor progression and invasion. AIMM 13:30-37, 2005
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14. Man YG, Zhang Y, Shen T, Vinh TN, Zeng X, Tauler J, Mulshine JL, Strauss BL. cDNA expression profiling identifies elevated expressions of tumor progression and invasion related genes in cell clusters of in situ breast tumors. Breast Cancer Res Treat 89:199-208, 2005.
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16. Halbwedi I, Ullmann R, Kremser ML, Man YG, Isadi-Moud N, Lax S, Denk H, Popper HH, Tavassoli FA, Moinfar F. Chromosomal alterations in low-grade endometrial stromal sarcoma and undifferentiated endometrial sarcoma as detected by comparative genemic hybridization. Gynecol Oncol 97: 582—587, 2005.
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20. Man YG, Sang QXA, Zhao CQ, Mannion C, Gardner WA. Focal basal cell degeneration induced lymphocyte infiltration is a potential trigger factor for prostate tumor invasion: implications for treatment and prevention. Cancer Detect Prev, Conditionally accepted
21. Man YG, Schwartz A, Levine P, Berg PE. BP1, a putative signature marker for inflammatory breast cancer. Conditionally accepted
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23. Man YG, Zhao CQ, Wang J, XL Chen. A subset of morphologically distinct prostate basal cells lacks corresponding immunophenotypic markers: Implications for clinical diagnosis. Submitted.
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b. Scientific papers near completion or in preparation

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tumor progression and invasion
2. Man YG, Simmens SJ. Focal myoepithelial cell layer disruptions induced tumor and stromal cell alterations correlate with an elevated frequency of invasion.
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43. Man YG. CD8 and mast cell tryptase positive cells are preferentially associated with focal myoepithelial cell layer disruptions: implications for breast tumor invasion. Proceedings of Department of Defense Breast Cancer Research Program Meeting P38-13,263, 2005
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